

## Chronic hepatitis C: Treat or wait? Medical decision making in clinical practice

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### Abstract

**AIM:** To analyze the decision whether patients with

chronic hepatitis C virus (HCV) infection are treated or not.

**METHODS:** This prospective cohort study included 7658 untreated patients and 6341 patients receiving pegylated interferon  $\alpha$ 2a/ribavirin, involving 434 physicians/institutions throughout Germany (377 in private practice and 57 in hospital settings). A structured questionnaire had to be answered prior to the treatment decision, which included demographic data, information about the personal life situation of the patients, anamnesis and symptomatology of hepatitis C, virological data, laboratory data and data on concomitant diseases. A second part of the study analyzes patients treated with pegylated interferon  $\alpha$ 2a. All questionnaires included reasons against treatment mentioned by the physician.

**RESULTS:** Overall treatment uptake was 45%. By multivariate analysis, genotype 1/4/5/6, HCV-RNA  $\leq$  520 000 IU/mL, normal alanine aminotransferase (ALT), platelets  $\leq$  142 500/ $\mu$ L, age > 56 years, female gender, infection length > 12.5 years, concomitant diseases, human immunodeficiency virus co-infection, liver biopsy not performed, care in private practice, asymptomatic disease, and unemployment were factors associated with reduced treatment rate. Treatment and sustained viral response rates in migrants (1/3 of cohort) were higher than in German natives although 1/3 of migrants had language problems. Treatment rate and liver biopsy were higher in clinical settings when compared to private practice and were low when ALT and HCV-RNA were low.

**CONCLUSION:** Some reasons against treatment were medically based whereas others were related to fears, socio-economical problems, and information deficits both on the side of physicians and patients.

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**Key words:** Hepatitis C virus; Interferon, Ribavirin; Liver cirrhosis; Migrants; Treatment barrier

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## INTRODUCTION

Approximately 170 million humans worldwide are estimated to have a chronic hepatitis C virus (HCV) infection including 400 000 in Germany<sup>[1,2]</sup>. More than 20 % of these patients will progress to cirrhosis, hepatocellular carcinoma, liver transplantation or death<sup>[3,4]</sup>. Therefore, all patients are candidates for antiviral therapy<sup>[5]</sup>. Its benefits need to be determined based on the individual's disease stage and on the likelihood of adherence and success<sup>[5,6]</sup>. Probably only 20 % of HCV-infected subjects know of their infection<sup>[3]</sup>. This diagnostic deficit is caused by various factors; e.g., physicians do not follow guidelines to screen for HCV infection when alanine aminotransferase (ALT) is elevated<sup>[7,8]</sup>. In addition only 11%-41% of known infections are treated<sup>[9-12]</sup>. Only some reasons for this therapeutic deficit have been identified including comorbidity, drug abuse and psychosocial factors<sup>[9,12-15]</sup>. Considering that therapy cures the disease in 50% of patients, treatment rate should be increased. The present study evaluates which factors influence the treatment decision in daily German practice.

## MATERIALS AND METHODS

The study which is ongoing was started in March 2003; the present data analyzes the treatment decision in patients included between March 2003 and May 2008. Throughout Germany 434 physicians (377 in private practice and 57 in hospital settings) contributed a mean number of 35 patients with chronic hepatitis C. The study included only one academic center. Basic data of the cohort have been published<sup>[16]</sup> and are only briefly mentioned here. The study was approved by health authorities and ethical committees. Due to its observational character it did not affect individual medical decisions. A structured questionnaire had to be answered prior to the treatment decision; a second part of the study analyzes patients treated with pegylated interferon  $\alpha$ 2a (Pegasys®, Roche Pharma AG) and ribavirin. This part is not fully analyzed here; only those aspects are analyzed which are relevant to the treatment decision. All questionnaires included rea-

**Table 1** Demographic data and basic characteristics

Characteristics	Not treated (n = 7658)	Treated (n = 6341)
% of the 13 999 patients	55.7	45.3
Genotypes 1/4/5/6 (%)	69.8	59.4
Genotypes 2/3 (%)	30.2	40.6
Age (yr, median)	44.0	41.0
BMI (kg/m <sup>2</sup> , median)	24.2	24.3
Gender (male %)	56.6	61.1
Regular employment (%)	35.3	50.2
Infection length (yr, median)	11.0	10.0
Ultrasound performed (%)	76.8	87.6
Liver biopsy performed (%)	12.8	30.2
Fibrosis score F 0-1	72.8	58.6
Fibrosis score F 2-4	27.2	41.4
Active drug or alcohol abuse (%)	28.3	13.8
HIV co-infection (%)	6.7	3.7
Psychiatric disease (%)	14.8	9.2
Severe language problems (%)	9.6	10.0
Initial HCV-RNA (IU/mL, median)	482 500	500 000
ALT (U/L, median)	61.0	78.0
Thrombocytes (/μL, median)	217 000	218 000
At least on concomitant disease (%)	62.3	42.6

BMI: Body mass index; HIV: Human immunodeficiency virus; HCV: Hepatitis C virus; ALT: Alanine aminotransferase.

sons against treatment mentioned by the physician. After July 2004 questionnaires also asked why patients denied therapy (n = 7658). Language skills were assessed after January 2006. Fibrosis was staged according to Desmet and Scheuer from F0 to F4<sup>[17]</sup>. Among the total 15 137 patients 7658 subjects did not receive any treatment ("untreated patients") while 6341 received pegylated interferon  $\alpha$ 2a and ribavirin ("treated patients") and 1138 alternative treatments. Details on alternative therapies (92.5% silymarin, 2.8% ursodesoxycholic acid, 4.9% other interferons) are not given because their characteristics were similar to the group receiving pegylated interferon  $\alpha$ 2a/ribavirin. Thus, in the following text the total cohort consists of 13 999 patients separated by the treatment decision into "treated patients" (n = 6341) and "untreated patients" (n = 7658). Specific procedures were not mandatory for inclusion except for documentation of chronic hepatitis C. There were no exclusion criteria except for patients below age 18 years and those with Child B/C cirrhosis. Thus, the study represents a real life scenario of a rather unselected cohort including a significant fraction of all patients diagnosed with hepatitis C in Germany.

### Statistical analysis

For continuous variables, receiver operating characteristic analyses estimated the best cut-off point for treatment decision; these cut-off points were 56 years for age, 520 000 IU/mL for basal HCV-RNA,  $\geq$  one concomitant disease,  $\geq$  12.5 years for infection length, and 142 500/ $\mu$ L for platelets. Categorical variables were used for continuous variables using these cut-off points. Association of various factors with treatment decision and sustained virological response (SVR = negative HCV-RNA 24 wk after end of therapy) were analyzed in an

Table 2 Treatment and sustained virological response rates in various subgroups

	Treatment rate %	SVR %	Number	Fischer's exact test, two-sides <i>P</i> value	
				Treatment rate	SVR
Total	45.3	49.6	13 999		
Genotypes 1/4/5/6	41.4	42.7	9114	< 0.0001	< 0.0001
Genotypes 2/3	52.7	59.8	4885		
Clinical setting	63.9	49.8	1298	< 0.0001	NS
Private practice	43.4	49.6	12 701		
Male	47.2	47.9	8214	< 0.0001	< 0.01
Female	42.6	52.3	5785		
Age ≤ 56 yr	49	51.3	11 497	< 0.0001	< 0.0001
Age > 56 yr	28.2	36.7	2502		
BMI ≤ 23 (kg/m <sup>2</sup> )	44.3	51.8	4762	< 0.01	< 0.05
BMI > 23 (kg/m <sup>2</sup> )	46.9	48.6	8846		
No employment	38.9	47.3	8113	< 0.0001	< 0.001
Regular employment	54.1	52	5886		
Bad German language skills	47	52.5	824	NS	NS
Good German language skills	45.8	47.8	7565		
Migrants	53.3	52.6	2663	< 0.0001	< 0.0001
German natives	41.7	45.4	5465		
Infection length ≤ 12.5 yr	62.8	51.6	3639	< 0.0001	< 0.01
Infection length > 12.5 yr	37.2	48	3165		
Ultrasound not performed	30.7	47.5	2568	< 0.0001	NS
Ultrasound performed	48.6	50	11 431		
Liver biopsy not performed	39.9	50.1	11 100	< 0.0001	NS
Liver biopsy performed	66.1	48.5	2899		
Fibrosis scores F0-1	60.9	52.4	1766	< 0.0001	< 0.01
Fibrosis scores F2-4	74.6	44.1	1017		
Clinical symptoms absent	42.2	47.8	4430	< 0.0001	NS
Clinical symptoms present	46.7	50.4	9569		
No concomitant disease	55.7	51.8	6527	< 0.0001	< 0.0001
At least one concomitant disease	36.2	46.8	7472		
Psychiatric disease absent	46.9	49.8	12 281	< 0.0001	NS
Psychiatric disease present	34.1	48.4	864		
Active drug or alcohol abuse absent	49.9	49.7	10 960	< 0.0001	NS
Active drug or alcohol abuse present	28.7	49.4	3039		
HIV co-infection absent	46.1	50	13 254	< 0.0001	< 0.01
HIV co-infection present	31.4	39.3	745		
Good quality-of-life	43.8	49.5	11 348	< 0.0001	NS
Reduced quality-of-life	51.8	50.1	2651		
ALT normal (< 50 U/L for men, < 30 U/L for women)	34.8	50.8	3297	< 0.0001	NS
ALT elevated (U/L)	49.6	49.7	10 105		
Thrombocytes ≥ 142 500 /μL	48	51.6	11 284	< 0.0001	< 0.0001
Thrombocytes < 142 500 /μL	38.9	36.2	1816		
HCV-RNA ≤ 520 000 IU/mL	45.4	54.8	6810	< 0.0001	< 0.0001
HCV-RNA > 520 000 IU/mL	49.7	43.3	5904		
No concomitant disease	55.7	51.8	6527	< 0.0001	< 0.0001
At least one concomitant disease	36.2	46.8	7472		
HIV co-infection absent	46.1	50	13 254	< 0.0001	< 0.01
HIV co-infection present	31.4	39.3	745		

SVR: Sustained virological response; BMI: Body mass index; HIV: Human immunodeficiency virus; ALT: Alanine aminotransferase; HCV: Hepatitis C virus; NS: Not significant.

univariate fashion using Fisher's exact test. Only those variables which were significant in the univariate analysis were included in the multivariate analysis.

## RESULTS

### Effects of various factors on treatment rate by univariate analysis

Basic characteristics of treated *vs* untreated patients are shown in Table 1. Many characteristics were similar for genotypes 1 (*n* = 8625), 4 (*n* = 440), 5 (*n* = 22) and 6 (*n*

= 27) and for genotypes 2 (*n* = 1000) and 3 (*n* = 3885) (data not shown); thus, further analyses were done in two subgroups, i.e., genotypes 1/4/5/6 *vs* 2/3. Table 2 summarizes treatment and SVR rates in the total cohort (45.3% and 49.6%, respectively) and in treated *vs* untreated patients.

By univariate analysis reduced treatment uptake and reduced SVR were seen in these groups: (1) genotypes 1/4/5/6 *vs* 2/3; (2) age > 56 years *vs* ≤ 56 years; (3) platelets ≤ 142 500/μL *vs* > 142 500/μL; (4) disease duration >12.5 years *vs* ≤ 12.5 years; (5) human im-

**Table 3** Treatment and sustained virological response rates *vs* socio-economic problems and concomitant diseases

Characteristics	Treatment rate %	SVR %	<i>n</i>
Drug abuse absent and employed without psychiatric disease or HIV co-infection	58.2	52.7	4382
Drug abuse absent and employed without psychiatric disease	58.2	52.4	4560
Drug abuse absent and employed	57.1	52.6	4929
Drug abuse absent	49.2	49.6	10 839
Drug abuse present	32.0	49.9	3160
Drug abuse present and unemployed	29.1	51.6	2203
Drug abuse present and unemployed with psychiatric disease	25.1	50.8	470
Drug abuse present and employed with psychiatric disease and HIV co-infection	7.1	0.0	56

HIV: Human immunodeficiency virus.

munodeficiency virus (HIV)/HCV co-infection *vs* HCV mono-infection; (6) presence *vs* absence of concomitant diseases; (7) German natives *vs* migrants; and (8) absence *vs* presence of regular employment.

Treatment uptake was reduced but SVR was higher in the following groups: (1) women *vs* men; (2) fibrosis F0-1 *vs* F2-4; and (3) basal HCV-RNA > 520 000 IU/mL *vs* ≤ 520 000 IU/mL.

Treatment uptake was reduced while SVR was similar in the following groups: (1) normal *vs* elevated ALT; (2) good *vs* reduced quality of life; (3) treatment in private practice *vs* clinical setting; (4) presence *vs* absence of psychiatric disease; (5) presence *vs* absence of alcohol or drug abuse; and (6) liver biopsy (and ultrasound) not performed *vs* performed.

History of *i.v.* drug abuse was the most frequent mode of infection (44.6%) followed by history of blood transfusions (17.0%). By multivariate analysis infection mode did influence neither treatment uptake nor SVR (data not shown). In the total cohort only 20.7 % of patients had a liver biopsy. Biopsy was done more often in genotypes 1/4/5/6 when compared to genotypes 2/3 (23.6% *vs* 15.3%,  $P < 0.001$ ) and in patients with elevated ALT (75.4% had elevated ALT) when compared to those with normal ALT (21.6% *vs* 18.4%,  $P < 0.05$ ). Biopsy rate was three-times higher in hospital settings when compared to practitioners (53.4% *vs* 17.4%,  $P < 0.001$ ). Alcohol or drug abuse was a frequent treatment barrier in particular in patients with psychiatric diseases or HIV co-infection and in jobless people (Table 2). Treatment rates were similarly low in drug abusers with or without substitution (data not shown). Patients with alcohol or drug abuse refused therapy less often compared to patients without abuse (50.2% *vs* 67.9%,  $P < 0.001$ ). Thus, the decision not to treat was made primarily by the physician. About 1/3 of all patients were migrants among whom 1/3 had severe language problems. Nevertheless, treatment and SVR rates were higher in migrants than in German natives while language problems did not affect treatment and SVR rates. Treatment uptake decreased with an increasing number of socio-economical and psychiatric problems; HIV infection on top of other problems reduced treatment uptake to 7 % (Table 3). SVR was unaffected even by presence of several socio-economical problems but was drastically reduced when there was a HIV co-infection on top of other problems.

### Multivariate regression analysis

Gender, age, genotype, HCV-RNA, ALT, platelets, symptoms, infection length, occupational status, concomitant diseases, HIV co-infection, alcohol and drug abuse, performance of liver biopsy and ultrasound, and quality-of-life significantly affected the treatment decision in the multivariate analysis (Figure 1). In patients with genotypes 1/4/5/6 the same factors as for the total cohort affected the treatment decision except for presence of symptoms; in patients with genotypes 2/3 the same factors as for the total cohort affected the treatment decision except for symptoms, platelets, employment, and performance of liver biopsy (data not shown). SVR was associated with various factors in the univariate analysis (Table 2). By multivariate analysis SVR was associated only with gender, genotype, HCV-RNA, age, platelets, symptoms, employment and HIV co-infection (data not shown).

### Analysis of specific reasons against treatment

The analysis looked at reasons mentioned by physicians and patients (Figure 2). The patients' wish was the most common reason against treatment (62.9 %). Among these patients lack of understanding the need of therapy, fear of side-effects, and problems with family and job were frequent reasons. Fear of side-effects was mentioned more often in women than in men (29.9% *vs* 18.8%,  $P < 0.001$ ). Alcohol or drug abuse and concomitant diseases (most commonly depression) were also frequent treatment barriers. Among patients who did not see a need for therapy reasons included lack of liver disease, symptoms, fibrosis and bad prognosis as well as normal ALT. In patients with normal ALT minor disease activity was mentioned by the physician as a reason to wait in 24.1% whereas this reason was mentioned in only 6.6% when ALT was elevated ( $P < 0.001$ ). In contrast, a similar percentage of patients mentioned the lack of disease activity as a treatment barrier irrespective of whether ALT was normal or elevated (27.1% *vs* 24.4%; NS). In patients with a HCV-RNA ≤ 520 000 IU/mL minor disease activity was mentioned by the physician as a reason to wait in 15.8% whereas this reason was mentioned in only 6.7% when HCV-RNA was > 520 000 IU/mL ( $P < 0.01$ ). The percentage of patients mentioning lack of disease activity as a treatment barrier was similar when looking at high or low HCV-RNA (data not shown). In patients who had liver biopsy minor disease activity was mentioned by the

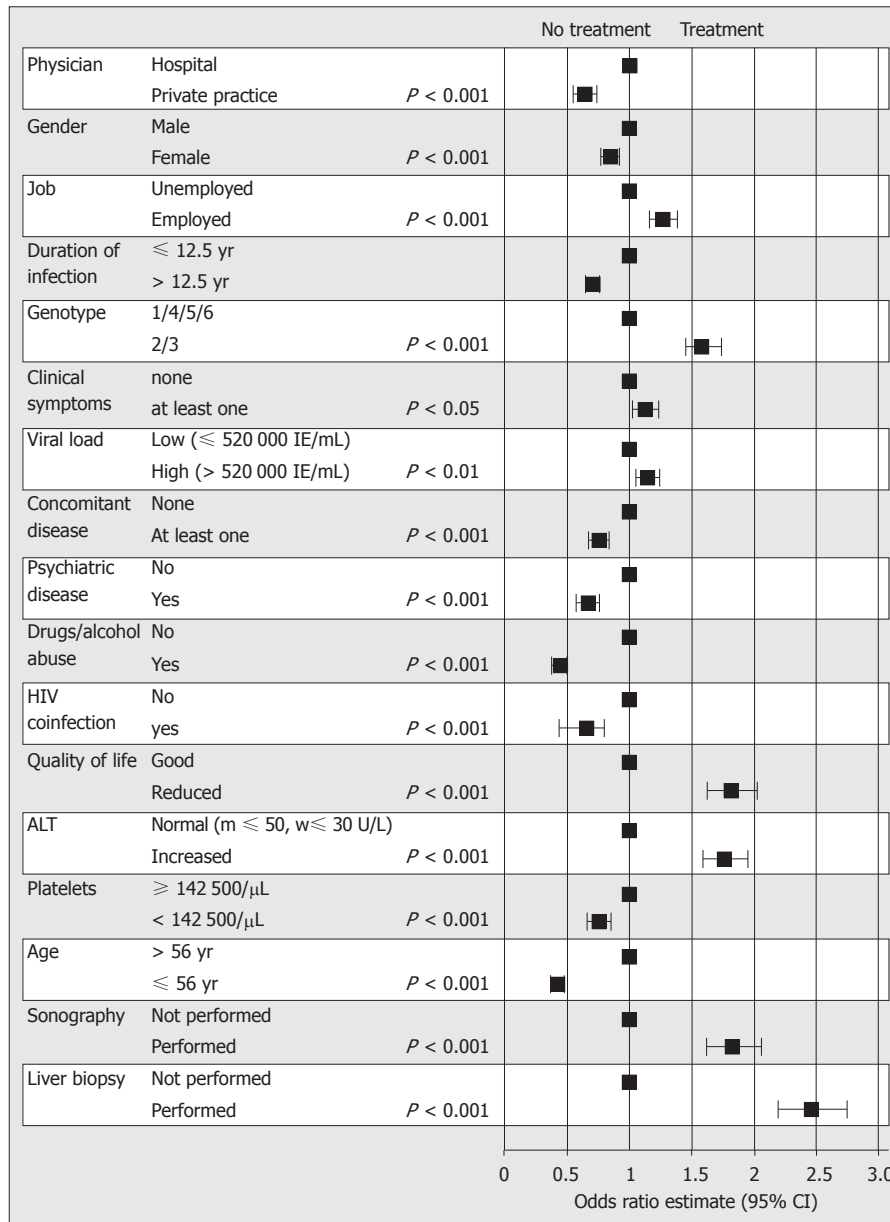


Figure 1 Multivariate regression analysis of treatment rates vs various factors. HIV: Human immunodeficiency virus; ALT: Alanine aminotransferase.

physician as a treatment barrier in 21.4 % whereas this reason was mentioned in only 10.3 % of patients without a liver biopsy ( $P < 0.01$ ). Patients mentioned fear of side effects and lack of understanding the need for therapy less often when treated in hospital settings as compared to private practice (18.5% vs 24.1% and 17.4% vs 25.9%,  $P < 0.01$ , respectively). In patients with drug/alcohol abuse, this abuse was the main treatment barrier mentioned by physicians (48.1 %). In contrast, patients with abuse refused therapy less often than those without (50.2% vs 67.9%,  $P < 0.001$ ). In HIV co-infection concomitant diseases and drug/alcohol abuse were more frequent treatment barriers than in mono-infection (25.0% vs 16.6% and 25.2% vs 16.4%,  $P < 0.01$ ). HIV co-infected patients refused therapy less often than mono-infected patients (59.1% vs 63.2%,  $P < 0.05$ ). Similarly, in patients with psychiatric diseases, the psychiatric disease was the main

treatment barrier (46.2%); among patients with psychiatric disease drug and alcohol abuse was another common barrier (24.5% vs 15.7% in patients without psychiatric disease;  $P < 0.001$ ). Older age was associated with a reduced treatment rate (49.0% vs 28.2% in patients ≤ 56 years vs patients > 56 years) (Table 2; Figure 1); in patients aged between 65 and 70 years treatment rate was 26.3% (158/600) and thus similar to the rate of 28.2% seen at ages > 56 years.

## DISCUSSION

Treatment uptake in the present cohort (45%) is one of the highest reported in the literature. Since the cohort included a significant fraction of all HCV-infected patients in Germany, the high treatment rate is probably not due to selection bias. In the literature treatment uptake

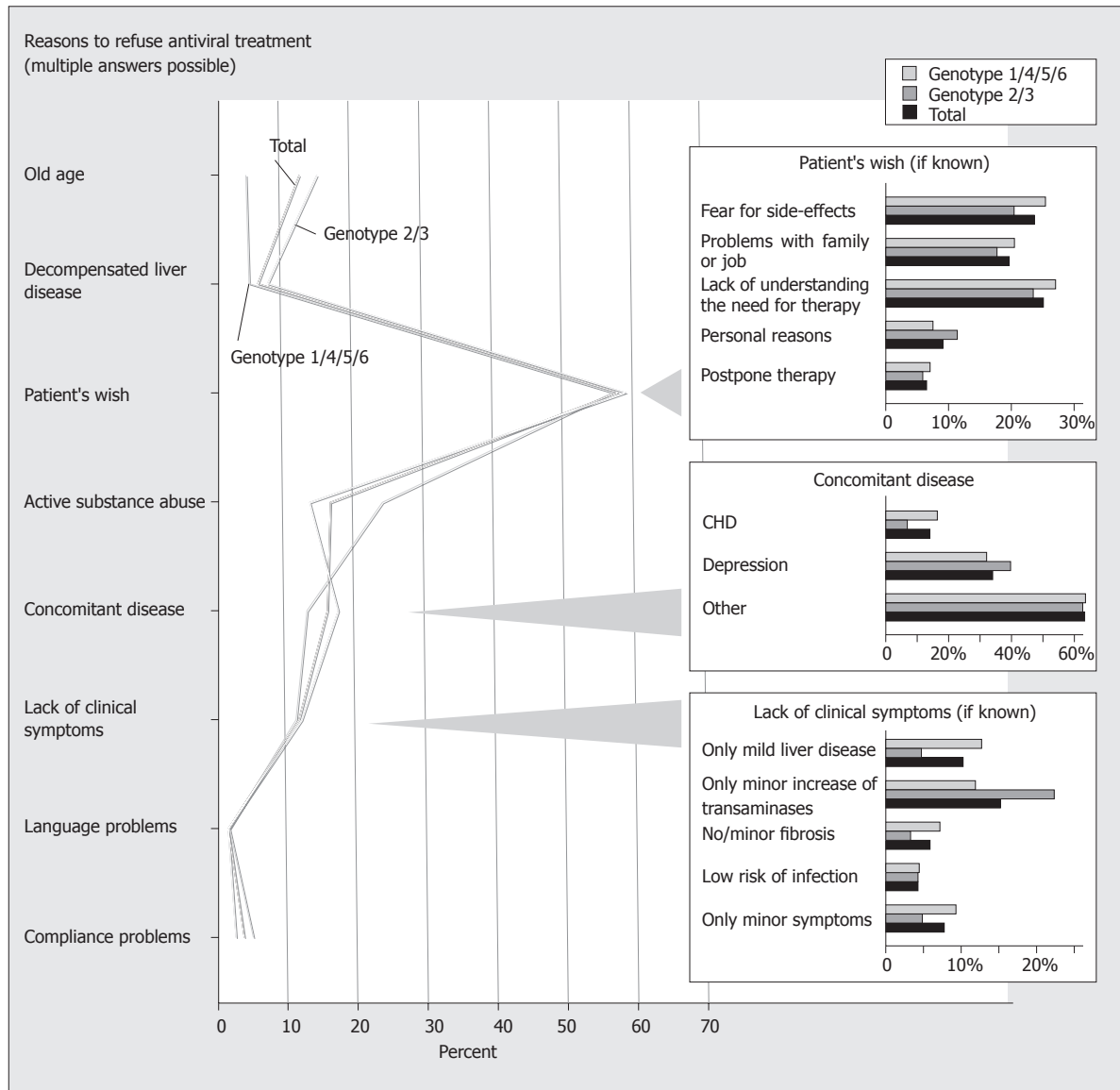


Figure 2 Reasons to refuse antiviral treatment.

tends to decrease with increasing number of subjects studied<sup>[9,12-15,18]</sup> with the lowest rate of 12% reported for the largest group of subjects studied<sup>[15]</sup>. There is little pre-selection in the present cohort; only patients with Child B/C cirrhosis were excluded as well as those under age 18 years. The present study did not include a relevant number of academic centers where most previous studies had been done. The community-based character of the present cohort incorporating 434 physicians and hospitals throughout the country reflects daily life in Germany probably better than looking at academic centres. However, one needs to keep in mind that most of the 434 physicians were not general practitioners, but gastroenterologists or at least physicians who treat hepatitis C. In general practitioners treatment rates may be lower than the 45% reported here. In the general United States community only 11% of all HCV-infected subjects had been treated<sup>[15]</sup>. This low treatment uptake suggests that therapeutic deficits are located on level of the general practitioner or

the health care system itself<sup>[7,8]</sup>. Recent studies show that knowledge deficits and misperceptions are main treatment barriers<sup>[19-21]</sup>. A high treatment rate might therefore reflect good knowledge among physicians and patients. In Germany most physicians who treat hepatitis C in private practice are organized in the Association of German Gastroenterologists (“bng”). Via their association gastroenterologists have been involved in the development of national HCV guidelines<sup>[6,22]</sup>. Many of them are members of the national “hepatitis competence network”. Recent studies have also shown that German patients with hepatitis C are well informed and better than patients with hepatitis B<sup>[23-25]</sup>. However, some practice aspects did not meet standards in the present cohort including the use of liver biopsy and interpretation of HCV-RNA values. Also, there were misperceptions among patients. Patients’ refusal was a common treatment barrier in the present cohort and in previous studies<sup>[9-11]</sup>. One of the highest treatment rates (41%) was published by Delwaide *et al.*<sup>[9]</sup>;

in that study only 17% of patients declined therapy. Thus, a high treatment uptake may be associated with low rate of refusal by patients<sup>[9]</sup>. This association may partly be explained by information deficits. In some subgroups, e.g., in patients with HIV co-infection and those with drug and alcohol abuse, the decision against treatment was often made by the physician whereas patients were rather willing to receive therapy.

Genotype and viral replication are major factors for estimating the chance for SVR and are therefore considered in the treatment decision. Correspondingly treatment rate and SVR were higher for genotypes 2/3 when compared to genotypes 1/4/5/6. In accordance with most previous studies<sup>[5,11,15,22]</sup> older age was associated with both reduced treatment uptake and reduced SVR in the present cohort. These results are in contrast to a recent study<sup>[18]</sup> in which being elderly was not associated with a low SVR. Surprisingly, treatment rate was low in patients with low HCV-RNA. This is a paradox because SVR is low at high replication in the present study and in the literature<sup>[26-28]</sup>. Thus, there may be misperceptions that high viral load indicates bad prognosis. All evidence shows this is not the case<sup>[22,29,30]</sup>. Further analyses suggested that physicians (and not patients) carry this misperception.

For many years normal serum aminotransferases were a common treatment barrier because they were thought to indicate good prognosis and reduced efficacy of therapy. In the meantime it has been shown that up to 30% of patients with normal ALT have major fibrosis and that SVR is not associated with ALT as also seen in the present study<sup>[22,29-31]</sup>. Despite this data, treatment rate was markedly lower in patients with normal ALT when compared to those with elevated ALT. We have reported a similar misperception of ALT for the decision to do HCV antibody tests<sup>[8]</sup>; many physicians just tested for HCV infection if ALT was markedly increased although most infections were associated with normal or slightly elevated ALT. Thus, ALT values are overestimated both in diagnostic<sup>[8]</sup> and treatment decisions<sup>[9,12]</sup>.

In contrast to academic trials, only 20% of patients had a liver biopsy in daily German practice. According to guidelines liver biopsy should be considered when the results will influence the treatment decision and in particular when treatment is not initiated<sup>[5,22]</sup>. However, treatment rate in patients with a liver biopsy was twice that seen in patients without a biopsy; according to guidelines it should be the other way around. Only a single previous study has also shown a positive association between performance of liver biopsy and treatment uptake<sup>[32]</sup>. It may be speculated that patients who refused liver biopsy may have a general problem to accept medical means. However, further analyses support other explanations. Biopsy rate in hospital settings was more than three-times higher than that in private practice. Although non-invasive means of assessing fibrosis are entering clinical routine, only a minority of community-based physicians use serum markers or sonographic stiffness in daily clinical routine as yet. Thus, physicians in private practice underestimate the value of liver biopsy more often than physicians in hospital

settings. The lack of immediate availability of biopsy may explain the low biopsy rate among practitioners. Also, treatment uptake was markedly lower for patients treated in private practice when compared to hospital settings. The analysis of specific reasons against treatment may partly explain this difference: patients mentioned fear of side effects and lack of understanding the need for therapy less often when treated in clinical settings when compared to private practice.

The treatment rate of HCV infection was considerably lower in HIV co-infected patients when compared to HCV mono-infection. Although SVR rates were also somewhat lower in co-infected patients, they were still in an acceptable range considering that end-stage liver disease is a common cause of death in HIV/HCV co-infection<sup>[33-35]</sup>. When compared with the literature the present rates of treatment and SVR (31% and 39%) look favorable. In other studies SVR ranged from 8% to 40% in co-infected patients<sup>[36-38]</sup>. Nevertheless HIV co-infection was a main treatment barrier also in the present cohort. Among co-infected patients drug and alcohol abuse as well as fear of side-effects were frequent treatment barriers. The present analysis also shows that HIV/HCV co-infected patients refused therapy less often than mono-infected patients; thus the low treatment rate is probably mainly caused by physicians and not by patients. In previous studies only 12%-33% of HIV co-infected patients initiated HCV therapy<sup>[36,39-40]</sup>; main barriers were non-adherence, patients' refusal, drug abuse and psychiatric problems. The present results demonstrate that the HIV infection on top of psychiatric and socio-economical problems may not only reduce treatment uptake but almost eliminates chances for SVR.

Recently it has been shown that HCV infection can successfully be treated in patients with drug and alcohol abuse and in those with HIV co-infection provided that there is a good management<sup>[35-38,41-43]</sup>. This is of great importance because alcohol abuse and co-infections accelerate fibrosis<sup>[34,35,44,45]</sup>. Although a history of drug abuse did not reduce treatment rate in the present cohort, active alcohol and drug abuse were associated with a markedly reduced treatment uptake as reported previously<sup>[10,11,14,15]</sup>; SVR was not affected by abuse. In 50% of abusers, physicians specified the abuse as the main treatment barrier. In contrast, patients with alcohol or drug abuse refused therapy less often than did patients without abuse. Thus, the decision not to treat was made primarily by the physician. A survey of 320 American Society of Addiction Medicine physicians showed that even among these specialists only a minority were providing HCV treatment or willing to provide treatment<sup>[46]</sup>. Treatment rates are even lower in the general community and may approach values of less than 1% in unselected drug addicts<sup>[47]</sup>.

Treatment rate was lower in unemployed patients when compared to those with a job while SVR was similar between these groups. Since jobless people tend to have a low educational state, these results fit to recent United States data showing that psychosocial factors and low education were associated with reduced treatment up-

take<sup>[12,14,48]</sup>. In the present cohort 1/3 of HCV infected patients were migrants among whom 1/3 had severe language problems. Unexpectedly, treatment uptake was not lower but higher in migrants when compared to German natives. These results can not be explained easily. Along this line women had a lower treatment rate when compared to men in this cohort as well as in another previous study<sup>[10]</sup>. This is also unexpected because men have a lower use of medical services than women both in the United States<sup>[49]</sup> and in Germany<sup>[50]</sup>. Thus, good knowledge and care about health issues *per se* do not necessarily increase treatment uptake for hepatitis C.

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## COMMENTS

### Background

In recent surveys only 20% of hepatitis C virus (HCV)-infected subjects know of their infection and only 20% of the latter are treated. Considering that therapy cures the disease in 50% of patients, treatment rate should be increased.

### Research frontiers

Bio-epidemiological research focuses to identify treatment barriers in patients with chronic hepatitis C. As yet only some reasons for the current large therapeutic deficit have been identified including co-morbidity, drug abuse and psychosocial factors. The present study evaluates which factors influence the treatment decision in daily German practice.

### Innovations and breakthroughs

Treatment uptake in the present cohort (45%) is one of the highest reported in the literature. A high treatment rate usually reflects good knowledge among physicians and patients. In Germany many physicians who treat hepatitis C are members of the national "hepatitis competence network" which is aimed to implement practice guidelines in the broad medical community. Despite the obvious success of the German hepatitis competence network some practice aspects did not meet standards in the present cohort including the use of liver biopsy and interpretation of HCV-RNA and alanine aminotransferase (ALT) values. Liver biopsy and thus knowledge about fibrosis stage were too low in particular in patients treated in private practice and in those with normal ALT. Also, there were misperceptions among patients as their refusal was a common treatment barrier. Unexpectedly, therapy uptake was higher in migrants despite language problems. Some further reasons against treatment appeared medically based whereas others seemed to be based on fears, socioeconomical problems and information deficits both on the side of physicians and patients.

### Applications

The present cohort study includes a significant fraction of all HCV-infected patients in Germany. The community-based character of the present cohort incorporating 434 physicians and hospitals throughout the country reflects daily

life in Germany probably better than looking at specialized academic centres.

### Terminology

Treatment barrier: Reasons why patients with chronic hepatitis C are not treated with antiviral drugs.

### Peer review

This is an important paper with a large HCV patient cohort from Germany including both academic and non-academic centres detailing reasons for treating and not treating HCV.

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